Kidney International, Vol. 20 (1981), pp. 723–727

Endarterial urokinase in childhood hemolytic uremic syndrome

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The use of thrombolytic drugs in children with hemolytic uremic syndrome (HUS) is a contentious topic. Although systemic streptokinase therapy has been reported to reduce both early mortality [1] and late sequelae, particularly hypertension [2, 3], carefully controlled trials are lacking. The efficacy of this relatively dangerous treatment has been difficult to assess since the mortality rate for HUS in recent years has fallen, coincident with the early and more skillful application of intensive care techniques, particularly peritoneal dialysis [4, 5]. We have suggested previously that the local infusion of drugs into the renal arteries of children with HUS, in conjunction with serial assessment of renal perfusion by scanning and arteriographic techniques, might allow a safe and controlled evaluation of their efficacy [6]. The present paper describes our experience with urokinase administered in this way to 8 children with severe HUS.

Methods

Clinical data are shown in Table 1. Seven children were referred from other hospitals for management of acute renal failure; case 5 was admitted directly from home. All had microangiopathic hemolytic anemia with red cell fragmentation on blood films and evidence of intravascular coagulation. Each had developed renal failure following a prodromal illness lasting up to 14 days, with symptoms referable to either the upper respiratory or gastrointestinal tract. The 8 children represent half of those with HUS referred to us between 1974 and 1978. They were selected for urokinase infusion because of anuria or oliguria, with evidence of markedly impaired renal perfusion on dynamic renal scanning. All were treated with hemodialysis or peritoneal dialysis (begun at the referring hospital in patients 2 and 6), and each received repeated blood transfusions. Other aspects of our management of acute renal failure in children have been described in other studies [7]. One child in the present study has been previously reported [6]. The mortality rate was 12% for children with HUS referred during the period of the study but not considered sufficiently ill to be treated with urokinase.

Urokinase administration. With the child sedated, a femoral artery was catheterized percutaneously using the Seldinger technique, and the catheter (polyurethane or polyethylene) advanced and manipulated to lie in a renal artery. Following renal arteriography (bilateral in 7 patients and unilateral in 1) a continuous infusion of urokinase (Urokinase, Leo Laboratories Ltd, Hayes, Middlesex, UK) was given into one renal artery via the indwelling catheter. The external diameter of the catheter varied from 1.2 to 2.2 mm; the ratio of the catheter diameter to the renal arterial lumen, as measured from the arteriogram, varied from 0.31 to 0.56. Urokinase was begun within 72 hours of admission, except in patients 2 and 6 where this interval was 9 and 21 days, respectively. The initial scans in these children showed only mild impairment of perfusion. Patients 6 and 7 subsequently received a bilateral infusion of urokinase after intervals of 21 and 0 days, respectively. The dosage and duration of the infusions are shown in Table 1. In addition to urokinase, all children received a low dose of heparin, 100 to 250 U/kg of body wt per 24 hours, subcutaneously in 5 cases and by the endarterial infusion in patients 1, 2, and 7. Three children also received oral dipyridamole, 10 mg/kg of body wt per 24 hours. These additional therapies were continued until the blood film no longer showed microangiopathy.

Early assessment. Renal blood flow was assessed in all patients by imaging with a gamma camera after the i.v. bolus injection of 99m technetium-labeled diethylenetriamine pentacetic acid (DTPA) [8]. Images were recorded on Polaroid or X-ray film during the first 30 sec after injection and at 2, 5, 10, 15, 20, and 30 min. These studies were performed before, during, and following the urokinase infusion. Each individual study was interpreted by one of us independently of clinical information. Renal perfusion was graded as improved, unaltered, or deteriorated.

Renal arteriography was repeated bilaterally in 4 children and in 1 child on the infused side only. In 3 patients urokinase was continued after the second arteriogram; in one of these further arteriography was obtained at the end of the infusion. Renal vessel caliber and filling of peripheral vessels were assessed in each child retrospectively by one of us independently of clinical information. Changes were graded as improved, unaltered, or deteriorated.

Late assessment. Among the children observed, 3 died. Of the 5 surviving children, 4 were seen 1 to 5 years after initial presentation. Evaluation included clinical examination, measurement of blood pressure, and urinalysis. Glomerular filtration rate was estimated from the clearance of intravenously administered ^{51}Cr-EDTA [9], and divided renal function was measured 3 hours after an i.v. injection of 99m Technetium-labeled dimercaptosuccinic acid (DMSA) by static scanning

Received for publication April 13, 1981

0085-2538/81/0020-0723 $01.00

Table 1. Clinical data on referral and details of urokinase infusion

Patient no.	Age *years*	Hemoglobin[a] *g/dl*	Platelets $\times 10^3/mm^3$	FDP titer[b] (normal < 1/5)	Reptilase time (control 12 to 13 sec)	Serum urea *mmoles/liter*	Serum creatinine μmoles/liter	Days from Guy's admission to onset of urokinase infusion, (no. of days at referring hospital)	Urokinase dosage, *Ploug units per 24 hr*	Duration of urokinase infusion, *hours*
1	0.2	8.4	34	1/40	19	22	303	1 (13)	25,000	120
2	1.7	4.2	167	1/5	22	86	445	9 (4)	50,000[c]	96
									75,000	72
3	4.0	5.5	10	1/20	32	87	727	2 (5)	100,000[d]	48
4	4.2	8.7	95	—	18	136	1415	< 1 (1)	75,000[d]	96
5	5.8	4.6	97	—	16	120	1600	< 1 (−)	100,000	72
6	6.7	6.7	97	1/5	13	49	490	21 (30)	100,000	48[e]
										168
7	9.9	5.0	14	1/40	23	37	596	3 (2)	100,000[d]	72[e]
										48
8	13.4	8.5	140	1/10	20	65	585	2 (2)	100,000	168

[a]All cases showed red cell fragmentation on blood film.
[b]FDP = fibrin degradation products.
[c]Dosage increased after first 96 hours of infusion.
[d]Also received oral dipyridamole.
[e]Unilateral (*a*) followed by bilateral (*b*) infusion.

Table 2. Early assessment of effects of urokinase on renal perfusion

Patient no.	DTPA scintigraphy			Renal arteriography		
	Initial	During urokinase	Following urokinase	Initial	During urokinase	Following urokinase
1	No perfusion or function on either side	No change	Bilateral equal improvement 3 weeks later	Equally poor perfusion bilaterally	—	—
2	Bilateral equally severe impairment	No change	Bilateral equal improvement 7 days later	Equally poor perfusion bilaterally	Deterioration on infused side, no change on noninfused side	Further deterioration on infused side
3	Bilateral severe impairment, worse on infused side	—	Bilateral equal improvement 12 days later, infused side remaining worse	Poor perfusion, infused side worse	—	—
4	Bilateral equally severe impairment	No change	Bilateral equal improvement 5 days later	Poor perfusion, only infused side studied	—	Deterioration, only infused side studied
5	Bilateral severe impairment, worse on infused side	No change	Bilateral equal improvement 2 days later, infused side remaining worse	Poor perfusion, infused side worse	—	—
6[a]	Bilateral moderate impairment, worse on non-infused side	No change during unilateral infusion; equal improvement during bilateral infusion	No change	Poor perfusion, noninfused side worse	—	Improvement on noninfused side only
7[a]	Bilateral equally severe impairment	No change during unilateral or bilateral infusion	Bilateral equal improvement 1 day later	Equally poor perfusion bilaterally	Bilateral equal improvement[b]	—
8	Bilateral severe impairment, worse on infused side	Transient bilateral improvement, especially on infused side	Equal bilateral deterioration	Equally poor perfusion bilaterally	Bilateral equal improvement	—

[a] Unilateral followed by bilateral urokinase infusion; arteriography performed after unilateral infusion.
[b] Catheter noted to have slipped out of renal artery into descending aorta.

using a gamma camera interfaced to a dedicated minicomputer [10]. The kidneys of 2 of the 3 children who died were examined post-mortem; in the third child permission for post-mortem was refused. The kidneys of the fifth surviving child were examined following bilateral nephrectomy prior to renal transplantation. Detailed histological comparisons between the treated and untreated kidneys were not available.

Results

In all children the initial DTPA scans showed evidence of impaired renal perfusion, with decrease or delay in the arterial phase following tracer injection. The renal arteriographic appearances were of diminished arterial caliber and impaired filling of peripheral vessels. The changes following urokinase infusion are summarized in Table 2. In only one child, patient 8,

Table 3. Late assessment in 4 survivors

Patient no.	Followup *years*	Urinary protein (> 200 mg per 24 hrs)	Hypertension	GFR *ml/min/1.73 m²*	Divided renal function on DMSA scintigraphy[a]	
					Urokinase-treated kidney *%*	Untreated kidney *%*
3	2.5	–	–	94	43	56
4	3.3	+	–	107	53	46
7	4.9	–	–	102	56/44[b]	—
8	1.2	+	+	5	40	59

[a]Difference of greater than 10% between kidneys is considered significant.
[b]Received unilateral followed by bilateral urokinase infusion; 56% of function contributed by kidney receiving least urokinase.

did serial DTPA scans suggest greater improvement in blood flow to the infused kidney compared to the noninfused kidney. However, this difference was not maintained subsequently and was not confirmed by repeat arteriography, which showed equal improvement in the vascular pattern bilaterally.

Serial estimations of thrombin and reptilase times, and fibrin degradation products, did not show any changes during urokinase infusion to suggest a systemic fibrinolytic effect on the coagulation system. No significant change in hemoglobin or platelet count occurred (Student's *t* test). No immediate morbidity associated with the use of the endarterial catheter was noted.

Followup data in 4 of the survivors are shown in Table 3. All survivors except one had recovered normal renal function. There was no evidence of greater recovery of function in the treated compared to the untreated kidney. In patients 3 and 8 the divided function from the DMSA scan showed a greater contribution to overall renal function from the non-infused kidney. However, in both of these children DTPA scans at presentation had suggested that the non-infused kidney had been less severely affected (Table 2). In patient 7, who had received a unilateral followed by a bilateral infusion, patchy uptake of DMSA suggested bilateral renal cortical scarring. In patient 8 recovery of renal function was sufficient to allow discontinuation of maintenance hemodialysis 13 months after presentation, at which time the GFR was 5 ml/min per 1.73 m^2. One year later it had risen further to 23 ml/min per 1.73 m^2, but there was persistent hypertension.

One child, patient 2, died 9 months after presentation. She was in chronic renal failure, severely hypertensive, with a left hemiplegia. A CAT scan showed cerebral infarction. During the postmortem examination, the infused kidney weighed 17 g; the noninfused kidney, 18 g.

Figure 1 shows the postmortem appearance of the kidneys of patient 1, who died of progressive renal failure and neurological complications 3 months after presentation. The infused kidney was considerably smaller than the noninfused kidney (weights not available). The ratio of the diameter of the endarterial catheter to the renal arterial lumen in this case was 0.56.

Patient 5 died 2 months after presentation, also from renal failure and neurological damage. Permission for a postmortem examination was refused.

Patient 6, who had received a unilateral followed by bilateral urokinase infusion, underwent bilateral nephrectomy because of hypertension, prior to renal transplantation 10 months after initial presentation. The kidney originally infused weighed 25 g and the contralateral kidney, 27 g.

Discussion

Controlled trials of streptokinase in childhood HUS have been widely advocated but difficult to design [11], and the significant incidence of serious bleeding during systemic treatment [2, 11] has made this therapy unacceptable to some [12]. The present study was performed in an attempt to overcome these problems by giving the non-antigenic thrombolytic agent urokinase by a low dosed infusion directly into one renal artery, thereby avoiding systemic effects and enabling the non-infused kidney to serve as a control. Renal scanning allowed assessment of both the immediate and long-term effects of treatment.

The encouraging therapeutic potential for locally infused urokinase suggested by our previous case report [6] was not confirmed by the present study, which failed to demonstrate any beneficial effects. In one patient (8) DTPA scan did suggest initially greater improvement in renal blood flow on the treated side; however, this difference was not maintained during further urokinase administration, and it was not confirmed by repeated renal arteriography. In addition, assessment one year later showed that the infused kidney contributed less to overall renal function than the noninfused side. The greater improvement in renal blood flow on the untreated side, observed also in patient 3, might have reflected the greater severity of involvement of the infused kidney at the time of presentation (the initial DTPA scans suggested such a disparity in these two cases). However, it is also possible that the presence of an indwelling catheter may have impaired renal blood flow and subsequent recovery of function, although DTPA scans did not show any diminution of perfusion following placement of the catheter. However, the possibility that the presence of the catheter may have impaired renal blood flow is suggested also by the shrunken appearance of the treated kidney during the postmortem examination in patient 1 (Fig. 1), in which the kidneys had appeared equally affected at presentation, and the catheter had been largest in relation to the renal arterial lumen.

Optimum dosage of urokinase for endarterial infusion in HUS is not known. We used a dose similar to that given by others to patients with HUS [13] and post-partum renal failure [14], and one which in the case of streptokinase has been found to successfully lyse intra-arterial thrombi in vivo [15]. The possibility that a significant systemic fibrinolytic effect, and therefore an effect on the contralateral kidney, might have occurred in the present study is unlikely in view of the stability of the coagulation tests during the infusion. Although a minor effect cannot be excluded, the dosage used was less than one tenth of that recommended for a systemic fibrinolytic effect in the treatment of pulmonary embolism [16].

Fig. 1. *Postmortem appearance of the kidneys in patient 1.* The smaller, contracted, scarred kidney on the right is the one that received urokinase.

A factor that may compromise the success of any treatment in HUS is the delay between the onset of the disease and the initiation of treatment. In some children in the present study this delay was considerable and was increased by time spent at the referring hospital. However, even in those children who received urokinase early in their illness (less than 48 hours after presentation in patients 4 and 5) no benefit could be demonstrated.

Patients were selected for treatment with urokinase on the basis of severe disease and the possibility of impending renal cortical necrosis, suggested both clinically and by evidence from DTPA scan of severely impaired renal perfusion. The recovery of normal renal function without hypertension in 3 children underlines the difficulty in selecting at presentation those children most likely to benefit from potentially dangerous treatment. Also noteworthy is the delayed recovery of renal function in patient 8, who was able to discontinue maintenance hemodialysis 13 months after initial presentation.

The results of the present study failed to show that locally infused urokinase is of benefit in childhood HUS. Moreover, such treatment may be harmful. The study also failed to provide any corroborative evidence for the likelihood of a beneficial effect from systemic thrombolytic treatment. Our results do not enable us to comment on the possibility that systemic treatment may prevent the development of hypertension in surviving children [2, 3].

Mortality in the present small series of severely affected children was high. However, others have shown that with attention to supportive treatment, particularly the early institution of peritoneal dialysis, the mortality from childhood HUS can be reduced to 10% or less, even in severely affected children [5]. Finally, we agree with the view [12] that thrombolytic agents are not indicated in the management of this disease except where controlled trials are being undertaken in severe cases and where the hematological affects are being monitored closely.

Summary. Urokinase was given by unilateral infusion for 48–168 hours into the renal arteries of 8 children (0.2 to 13.0 years) with acute renal failure and impaired renal perfusion due to hemolytic uremic syndrome (HUS). Two children subsequently received a bilateral infusion. Immediate changes in renal perfusion were assessed by serial dynamic renal scanning in all patients and by repeat renal arteriography in 5. No improvement clearly attributable to urokinase was observed. In 4 surviving children assessment of divided renal function by static renal scanning 1 to 5 years after presentation showed no evidence of benefit from urokinase. Examination of the kidneys of 2 of the 3 children who died, and one who underwent bilateral nephrectomy prior to renal transplantation, showed no preservation of renal mass attributable to urokinase; in one of these children the infused kidney was considerably smaller than the untreated kidney. It is concluded that local infusion of urokinase had no beneficial effect on the course of HUS in these children.

Acknowledgments

We are grateful to Leo Laboratories Ltd., Hayes, Middlesex, England, who donated the urokinase used in this study and to Professor J.S. Cameron and Dr. M. Winter for help with the preparation of the manuscript. Dr. Jones has a lectureship funded by the British Kidney Patient Association, Dr. Morris holds a Commonwealth Medical Fellowship awarded by the Association of Commonwealth Universities.

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